Amendments to the Specification:

Please replace paragraph number **[0002]** with the following rewritten paragraph:

[0002] The present invention relates generally to osmotic delivery systems for delivering beneficial agents, and more particularly, to osmotic delivery system semipermeable body assemblies which control the delivery rate of a beneficial agent from an osmotic delivery system incorporating one of the semipermeable body assemblies.

Please replace paragraph number **[0004]** with the following rewritten paragraph:

[0004] FIG. 1 illustrates a ~~cross~~ cross-sectional view of a known osmotic delivery system 20. The osmotic delivery system 20, commonly referred to as an "osmotic pump," generally includes some type of a capsule or enclosure 22 having a semipermeable portion which may selectively pass water into an interior of the capsule which contains a water-attracting osmotic agent 24. In the known osmotic delivery system illustrated in FIG. 1, the walls of the capsule 22 are substantially impermeable to items within and outside the capsule, and the plug 26 acts as the semipermeable portion. The difference in osmolarity between the water-attracting agent 24 and the exterior of the capsule causes water to pass through the semipermeable portion of the capsule which in turn causes the beneficial agent 23 to be delivered from the capsule 22 through the delivery port 29. The water-attracting agent 24 may be the beneficial agent delivered to the patient; however, in most cases such as that illustrated in FIG. 1, a separate osmotic agent is used specifically for its ability to draw water into the capsule 22.

Please replace paragraph number **[0005]** with the following rewritten paragraph:

[0005] When a separate osmotic agent 24 is used, the osmotic agent may be separated from the beneficial agent 23 within the capsule 22 by a movable dividing member or piston 28. The structure of the capsule 22 is such that the capsule does not expand when the osmotic agent 24 takes in water and expands. As the osmotic agent 24 expands, it causes the beneficial agent 23 to be discharged through the ~~orifice~~ delivery port 29 at the same rate as the liquid, which is typically water, enters the osmotic agent 24 by osmosis. Osmotic delivery systems may

be designed to deliver a beneficial agent at a controlled constant rate, a varying rate, or in a pulsatile manner.

Please replace paragraph number **[0006]** with the following rewritten paragraph:

[0006] In the known osmotic delivery system 20 illustrated in FIG. 1, an osmotic tablet is used as the osmotic agent 24 and is placed inside the capsule 22. The membrane plug 26 is placed in an opening in the capsule 22 through which the osmotic tablet 24 and piston 28 were inserted. Known membrane plugs 26 are typically a cylindrical member with ribs, and operate in the same manner as a cork. These membrane plugs 26 seal the interior of the capsule from the exterior environment, essentially permitting only certain liquid molecules from the environment of use to permeate through the membrane plug into the interior of the capsule 22. The rate that the liquid permeates through the membrane plug 26 controls the rate at which the osmotic agent 24 expands and drives a desired concentration of beneficial agent 23 from the osmotic delivery system 20 through the delivery ~~orifice~~ port 29. The rate of delivery of the beneficial agent from the osmotic delivery system 20 may be controlled by varying the permeability coefficient of the membrane plug 26.

Please replace paragraph number **[0009]** with the following rewritten paragraph:

[0009] Many osmotic delivery systems which use membrane plugs, such as that illustrated in FIG. 1, must administer beneficial agents at rapid delivery rates over a short period of time. These known systems use membrane materials having high permeability ~~coefficients.~~ coefficients, i.e., high liquid uptake semipermeable materials. In general, high liquid uptake semipermeable materials are those that have greater than 60% water uptake, where % water uptake = 100 x (wet weight - dry weight)/dry weight. Thus, low uptake semipermeable materials have equal or less than 60% water uptake.

Please replace paragraph number **[0011]** with the following rewritten paragraph:

[0011] Even if the membrane plug does not dislodge from the capsule, some high liquid uptake membrane plugs permit the osmotic agent to leak from the capsule because the membrane materials are biologically unstable. For instance, some semipermeable membranes having high

permeability coefficients, such as organic polymer membranes, are unstable in biological environments and may degrade over time, permitting fluids, crystals, or powder within the interior of the capsule to leak to the environment of use. In some instances, the osmotic agent within the capsule may be harmful to the recipients of implantable delivery ~~system~~ systems, especially if released as a bolus, i.e., all at once at a single location.

Please replace paragraph number **[0014]** with the following rewritten paragraph:

[0014] Because of the above-identified problems associated with current osmotic delivery system membrane plugs, it is costly and particularly difficult to administer beneficial agents from osmotic delivery systems at different desired delivery rates. Known membrane plug designs control the permeation rate of the membrane and the beneficial agent delivery rate of the osmotic delivery system by selecting a different material membrane plug for each application requiring a particular beneficial agent administration rate. Additionally, current high liquid uptake membrane plugs may dislodge or leak, and may be unstable in biological environments, causing items in the interior ~~of~~ of the delivery capsule to harmfully leak to the environment of use. These problems associated with current osmotic drug delivery systems having known membrane plugs have created a need for a solution.

Please replace paragraph number **[0039]** with the following rewritten paragraph:

[0039] FIG. 1 is a ~~cross~~ cross-sectional view of a prior art osmotic drug delivery device which incorporates a membrane plug.

Please replace paragraph number **[0056]** with the following rewritten paragraph:

[0056] FIG. 17 is a partial sectional view of another osmotic delivery system according to the present invention having a semipermeable body and liquid impermeable sleeve, where the liquid impermeable sleeve is threaded on the enclosure of the osmotic delivery system and is ~~moveable~~ movable with respect to the semipermeable body.

Please replace paragraph number **[0058]** with the following rewritten paragraph:

[0058] FIG. 19 is a partial sectional view of another osmotic delivery system according to the present invention having a semipermeable body and a liquid impermeable sleeve that is threaded on the semipermeable body and ~~moveable~~ movable with respect to the semipermeable body.

Please replace paragraph number **[0074]** with the following rewritten paragraph:

[0074] As mentioned above, the osmotic delivery system plug 30 is made from a semipermeable body 32, which is formed from a semipermeable material. The semipermeable material of the body 32 allows liquids, especially water, to pass from an exterior environment of use into the capsule or enclosure 71 to cause the osmotic agent 78 to swell. However, the semipermeable material forming the semipermeable body 32 is largely impermeable to the materials within the capsule and other ingredients within the fluid environment. Semipermeable compositions suitable for the semipermeable body 32 are well known in the art, examples of which are disclosed in U.S. Patent No. 4,874,388, the entire disclosure of which is incorporated herein by reference. Such possible semipermeable materials from which the body 32 can be made include, but are not limited to, for example, Hytrel polyester elastomers (DuPont), cellulose esters, cellulose ethers and cellulose ester-ethers, water flux enhanced ethylene-vinyl acetate copolymers, semipermeable membranes made by blending a rigid polymer with water-soluble low molecular weight compounds, and other semipermeable materials well known in the art. The above cellulosic polymers have a degree of substitution, D.S., on the anhydroglucose unit, from greater than 0 up to 3 inclusive. ~~By,~~By "degree of substitution," or "D.S.," is meant the average number of hydroxyl groups originally present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a substituting group. Representative materials include, but are not limited to, one selected from the group consisting of cellulose acylate, cellulose diacetate, cellulose triacetate, mono-, di-, and tricellulose alkanylates, mono-, di-, and tricellulose aroylates, and the like. Exemplary cellulosic polymers include cellulose acetate having a D.S. up to 1 and an acetyl content up to 21%; cellulose acetate having a D.S. of 1 to 2 and an acetyl content of 21% to 35 %; cellulose acetate having a D.S. of 2 to 3 and an acetyl content of 35% to 44.8%,

and the like. More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propionyl content of 39.2% to 45% and a hydroxyl content of 2.8% to 5.4%; cellulose acetate butyrate having a D.S. of 1.8 and an acetyl content of 13% to 15% and a butyryl content of 34% to 39%; cellulose acetate butyrate having an acetyl content of 2% to 29%, a butyryl content of 17% to 53% and a hydroxyl content of 0.5% to 4.7%; cellulose acetate butyrate having a D.S. of 1.8, and acetyl content of 4% average weight percent and a butyryl content of 51%; cellulose triacylates having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate, and cellulose trioctanoate; cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dipentate; coesters of cellulose such as cellulose acetate butyrate and cellulose, cellulose acetate propionate, and the like.

Please replace paragraph number **[0077]** with the following rewritten paragraph:

[0077] Alternatively, the plug need not have a stop surface 36, as illustrated by the alternative embodiment of a plug or semipermeable body assembly 130 shown in FIG. 12. The foregoing and following discussion of the benefits and functions of the plug 30 also apply to the plug 130. Thus, the plug 130 is assigned corresponding reference numbers as the plug 30, increased by 100. The plug 130 also includes many additional features and inherent functions, as discussed below. The plug 130 may be inserted entirely within an opening of an enclosure of an osmotic delivery system because the ~~plug~~ plug 130 does not include a stop surface or head preventing complete insertion. When the plug 130 is completely inserted within the enclosure of an osmotic delivery system, the cylindrical flat surface or end surface 148 defines the liquid contact surface of the plug because it is immediately exposed to liquids when such an osmotic delivery system is placed in a liquid environment of use. The plug 130 may also be partially inserted into an opening of an osmotic delivery system enclosure such that the liquid contact surface includes more than just the end surface 148. The plug 130 includes a semipermeable body 132 that receives an insert 160, similar to the insert 60 described below.

Please replace paragraph number **[0079]** with the following rewritten paragraph:

[0079] As shown in FIG. 4A, the predetermined wall width *w* is defined by the location of the outer surface 38 relative to the interior surface 54, and the predetermined plug thickness *t* is defined by the location of the depth surface 50 relative to the liquid contact surface 48. Thus, the depth of the depth surface 50 within the semipermeable body 32, and the distance the interior surface 54 is from the longitudinal center axis C (or diameter 46 of the recess ~~52)~~ 52), determine the size of the hollow interior portion or recess 52 in the interior of the semipermeable body 32. Together, the predetermined wall width *w* and the predetermined plug thickness *t* define an "effective thickness" L of the semipermeable body. As described below, by varying the effective thickness L of the semipermeable body, the liquid permeation rate through the body can be controlled; this is beneficial because, for example, different desired liquid permeation rates through osmotic delivery system plugs 30 according to the present invention are obtainable from plugs formed from the same material having the same permeability coefficient and liquid uptake characteristics. This is further beneficial because biocompatibility and toxicity tests need only be performed on one semipermeable material.

Please replace paragraph number **[0085]** with the following rewritten paragraph:

[0085] Osmotic delivery system plugs 30 according to the present invention permit the administration of beneficial agents 72 from osmotic delivery systems at rapid delivery rates over a relatively short period of time, even though the plugs may use a semipermeable material which, as measured against previous membrane plugs, has a low permeability coefficient. These low permeability coefficient membrane materials do not have high liquid uptake characteristics, and do not swell as dramatically as high uptake materials when the liquid from the surrounding environment permeates through the membrane. Thus, the osmotic delivery plug ~~30~~ 30, that includes a hollow interior portion 52 sized for a fast liquid permeation ~~rate~~ rate, does not overly swell and creep out of the capsule, or permit the osmotic agent 78 to leak from the capsule. Furthermore, the osmotic delivery plug 30 may be made from materials that are stable in biological environments, and do not significantly degrade over time, which could permit fluids, crystals, or powder within the interior of the capsule 71 to leak to the environment of use.

Please replace paragraph number **[0089]** with the following rewritten paragraph:

[0089] The semipermeable body 32 is preferably injection molded. However, the semipermeable body may be fashioned by a different process. For example, the semipermeable body may also be made from extrusion, reaction injection molding, rotational molding, thermoforming, compression molding, and other known casting processes. Injection molding is preferable in that the ejector pin or core may be used to form the recess 52, and different length and sized ejector pins or cores may be easily changed to fashion different sized recesses to controllably vary the liquid permeation rate through the membrane body 32 of the plug 30. Additionally, the recess 52 may be formed in the semipermeable body 32 after the semipermeable ~~body~~ body 32 has been formed without a recess. For example, a cylinder of semipermeable material may be fabricated and sliced into smaller cylinders. Thereafter, a cylindrical section may be removed from the semipermeable body to form the recess 52 in the body. Thus, the liquid permeation rate through the semipermeable body 32 may be changed by first making a semipermeable body having a liquid permeability coefficient and a thickness, and then changing the thickness of the semipermeable body to alter the liquid permeation rate through the semipermeable body.

Please replace paragraph number **[0090]** with the following rewritten paragraph:

[0090] In one embodiment of the present invention, the semipermeable body 32 was formed by injection molding. The semipermeable material used in the injection molding process was TECOPHILIC HP60D-20. The following injection molding operating parameters were used to form the above described semipermeable ~~body.~~ body:

NOZZLE TEMP. ZONE 1	183°C	INJ. TIME	4 SEC.
BARREL TEMP. ZONE 2	180°C	HOLD TIME	2 SEC.
BARREL TEMP. ZONE 3	175°C	CLAMP CLOSED TIME	20 SEC.
BARREL TEMP. ZONE 4	170°C	SCREW SPEED	430 RPM
HOLDING PRESSURE	500 PSI	BACK PRESSURE	200 PSI
INJECTION PRESSURE	500 PSI		

Please replace paragraph number **[0094]** with the following rewritten paragraph:

[0094] It is also preferable that the insert 60 be substantially pervious to liquids, permitting the liquid which has permeated through the semipermeable body 32 to freely travel ~~though~~ through the insert to the osmotic agent 78 of the osmotic delivery system 70. It is preferable that the insert 60 be more pervious to liquids than the semipermeable membrane body 32 such that the liquid permeation rate through the semipermeable body 32 with the insert 60 therein is not substantially affected by the liquid permeability of the insert. In other words, the liquid permeation rate through the semipermeable body 32 should not change significantly because the insert 60 has been inserted into the recess 52. Because the insert 60 is preferably more pervious to liquids than the semipermeable body 32, the insert 60 will not adversely affect the liquid permeation rate through the semipermeable body 32 to any significant degree. Materials from which the insert 60 may be ~~fashion~~ fashioned include, but are not limited to, metals, glasses, and plastics which are fashioned with pores, holes or liquid channels. Preferred materials for the insert 60 are fritted glass or metal, and macroporous polymers.

Please replace paragraph number **[0096]** with the following rewritten paragraph:

[0096] Alternatively, the insert 60 may not be inserted into the recess 52. Although the insert 60 is preferred because it maintains the seal, instances may arise where the insert 60 is not necessary. For example, if the semipermeable body 32, according to an alternative embodiment of the present invention ~~not depicted~~ (not depicted), has a hollow interior portion 52 with a small recess diameter 46 and predetermined depth, the insert 60 may not be needed to assist in effecting the seal. Generally, the predetermined wall thickness *w* and the structural characteristics of the semipermeable body 32 determine whether ~~of~~ or not a rigid insert is needed to assist in effecting the seal, which is ~~determinable~~ capable of being determined by experimental methods well known in the art.

Please replace paragraph number **[00100]** with the following rewritten paragraph:

[00100] The osmotic drug delivery ~~device~~ system 70, as illustrated in FIG. 7, includes an elongated substantially cylindrical enclosure 71 having an opening 79 which, as illustrated in

FIG. 7, is plugged with the plug 30. The end of the enclosure opposite the opening 79 has one or more delivery ports 75 for delivering a beneficial agent 72 from the osmotic delivery system 70. The elongated enclosure 71 is formed of a material which is sufficiently rigid to withstand expansion of an osmotic agent 78 without changing size or shape. The enclosure 71 is preferably substantially impermeable to fluids in the environment as well as to ingredients contained within the osmotic delivery device such that the migration of such materials into or out of the device through the impermeable material of the enclosure is so low as to have substantially no adverse impact on the function of the osmotic delivery device.

Please replace paragraph number **[00102]** with the following rewritten paragraph:

[00102] The embodiment of the present invention illustrated in FIG. 7 includes an optional movable separating member or movable piston 74. The osmotic agent 78 within the enclosure 71 is separated from the beneficial agent 72 by the movable piston 74. The enclosure 71 receives the osmotic agent 78, which in the embodiment of the present invention depicted in FIG. 7 is one or more osmotic tablets. Osmotic ~~agents~~ agents 78, specifically the osmotic ~~tablet 78~~ tablet of the embodiment of the present invention ~~illustrated~~ illustrated in FIG. 7, drive the osmotic flow of osmotic delivery devices. However, the osmotic agent 78 need not be a tablet; it may be other conceivable shapes, textures, densities, and consistencies and still be within the confines of the present invention.

Please replace paragraph number **[00103]** with the following rewritten paragraph:

[00103] When used, the movable separating member or movable piston 74 is a substantially cylindrically member which is configured to fit within the enclosure 71 in a sealed manner which allows the piston to slide along a longitudinal direction within the enclosure. The piston 74 preferably is formed of an impermeable resilient material and includes annular ring shape protrusions 76 which form a ~~moveable~~ movable or sliding seal with the inner surface of the enclosure.

Please replace paragraph number **[00107]** with the following rewritten paragraph:

[00107] In general, typical materials of construction suitable for the enclosure 71 according to the present invention include ~~non-~~nonreactive polymers or biocompatible metals or alloys. The polymers include acrylonitrile polymers such as acrylonitrile-butadiene-styrene terpolymer, and the like; halogenated polymers such as polytetrafluoroethylene, polychlorotrifluoroethylene copolymer tetrafluoroethylene and hexafluoropropylene; polyimide; polysulfone; polycarbonate; polyethylene; polypropylene; polyvinylchloride-acrylic copolymer; polycarbonate-acrylonitrile-butadiene-styrene; polystyrene; and the like. Metallic materials useful for the enclosure 71 include stainless steel, titanium, platinum, tantalum, gold, and their alloys, as well as gold-plated ferrous alloys, platinum-plated ferrous alloys, cobalt-chromium alloys and titanium nitride coated stainless steel.

Please replace paragraph number **[00108]** with the following rewritten paragraph:

[00108] In general, materials suitable for use in the movable separating member 74 are elastomeric materials including the ~~non-~~nonreactive polymers listed above, as well as elastomers in general, such as polyurethanes and polyamides, chlorinated rubbers, styrene-butadiene rubbers, and chloroprene rubbers.

Please replace paragraph number **[00109]** with the following rewritten paragraph:

[00109] The osmotic ~~agent~~ agent 78, illustrated in FIG. 7 by ~~the~~ an osmotic ~~tablet 78~~ tablet, is a liquid-attracting agent used to drive the flow of the beneficial agent. The osmotic agent may be an osmagent, an osmopolymer, or a mixture of the two. Species which fall within the category of osmagent, i.e., the ~~non-~~nonvolatile species which are soluble in water and create the osmotic gradient driving the osmotic inflow of water, vary widely. Examples are well known in the art and include magnesium sulfate, magnesium chloride, potassium sulfate, sodium chloride, sodium sulfate, lithium sulfate, sodium phosphate, potassium phosphate, d-mannitol, sorbitol, inositol, urea, magnesium succinate, tartaric acid, raffinose, and various monosaccharides, oligosaccharides and polysaccharides such as sucrose, glucose, lactose, fructose, and dextran, as well as mixtures of any of these various species.

Please replace paragraph number **[00110]** with the following rewritten paragraph:

[00110] Species which fall within the category of osmopolymer are hydrophilic polymers that swell upon contact with water, and these vary widely as well. Osmopolymers may be of plant or animal origin, or may be synthetic, and examples of osmopolymers are well known in the art. Examples include: poly(hydroxy-alkyl methacrylates) ~~with~~ with a molecular weight of 30,000 to 5,000,000, poly(vinylpyrrolidone) ~~with~~ with a molecular weight of 10,000 to 360,000, anionic and cationic hydrogels, polyelectrolyte complexes, poly(vinyl alcohol) having low acetate residual, optionally cross-linked with glyoxal, formaldehyde or glutaraldehyde and having a degree of polymerization of 200 to 30,000, a mixture of methyl cellulose, cross linked agar and carboxymethylcellulose, a mixture of ~~hydroxypropl~~ hydroxypropyl ~~methyecellulose~~ methylcellulose and sodium carboxymethylcellulose, polymers of N-vinyllactams, polyoxyethylene-polyoxypropylene gels, polyoxybutylene-polyethylene block copolymer gels, carob gum, polyacrylic gels, polyester gels, polyurea gels, polyether gels, polyamide gels, polypeptide gels, polyamino acid gels, polycellulosic gels, carbopol acidic carboxy polymers having molecular weights of 250,000 to 4,000,000, Cyanamer polyacrylamides, cross-linked indene-maleic anhydride polymers, Good-~~Rite~~Rite® polyacrylic acids having molecular weights of 80,000 to 200,000, Polyox Polyethylene oxide polymers having molecular weights of 100,000 to 5,000,000, starch graft copolymers, and Aqua-~~Keeps~~Keeps® acrylate polymer polysaccharides.

Please replace paragraph number **[00111]** with the following rewritten paragraph:

[00111] The osmotic agent 78 may be manufactured by a variety of techniques, many of which are known in the art. In one such technique, an ~~osmotically~~ active osmotic agent 78 is prepared as solid or ~~semi-~~semisolid formulations and pressed into pellets or tablets whose dimensions correspond to slightly less than the internal dimensions of the respective chambers which they will occupy in the enclosure interior. Depending on the nature of the materials used, the agent and other solid ingredients which may be included may be processed prior to the formation of the pellets by such procedures as ballmilling, calendaring, stirring or rollmilling to achieve a fine particle size and hence fairly uniform mixtures of each. The enclosure 71 may be

formed from any of the wall-forming materials disclosed above by the use of a mold, with the materials applied either over the mold or inside the mold, depending on the mold configuration. Any of the wide variety of techniques known in the pharmaceutical industry may be used to form the enclosure 71.

Please replace paragraph number **[00112]** with the following rewritten paragraph:

[00112] In assembling the osmotic delivery device 70 according to one embodiment of the present invention, the piston 74 is first inserted into the enclosure 71. Once the osmotic agent ~~pellets or tablets~~ 78 in the form of pellets or tablets, has ~~have~~ been formed~~, they are~~ it is placed inside the preformed enclosure 71 on top of the separating member 74. Then the osmotic delivery system plug 30, according to one embodiment of the present invention, is placed into the opening 79 of the enclosure 71 to close off and seal one end of the osmotic delivery system.

Please replace paragraph number **[00118]** with the following rewritten paragraph:

[00118] Examples of drugs which may be delivered by devices according to this invention include, but are not limited ~~to~~ to, prochlorperzine edisylate, ferrous sulfate, aminocaproic acid, mecamylamine hydrochloride, procainamide hydrochloride, amphetamine sulfate, methamphetamine hydrochloride, benzamphetamine hydrochloride, isoproterenol sulfate, phenmetrazine hydrochloride, bethanechol chloride, methacholine chloride, pilocarpine hydrochloride, atropine sulfate, scopolamine bromide, isopropamide iodide, tridihexethyl chloride, phenformin hydrochloride, methylphenidate hydrochloride, theophylline cholinate, cephalexin hydrochloride, diphenidol, meclizine hydrochloride, prochlorperazine maleate, phenoxybenzamine, thiethylperzine maleate, anisindone, diphenadione erythrityl tetranitrate, digoxin, isoflurophate, acetazolamide, methazolamide, bendroflumethiazide, chloropromaide, tolazamide, chlormadinone acetate, phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole, erythromycin, hydrocortisone, hydrocorticosterone acetate, cortisone acetate, dexamethasone and its derivatives such as betamethasone, triamcinolone, methyltestosterone, 17-S-estradiol, ethinyl estradiol, ethinyl estradiol 3-methyl ether, prednisolone, 17-α-hydroxyprogesterone acetate, 19-nor-progesterone, norgestrel, norethindrone,

norethisterone, norethiederone, progesterone, norgesterone, norethynodrel, aspirin, indomethacin, naproxen, fenoprofen, sulindac, indoprofen, nitroglycerin, isosorbide dinitrate, propranolol, timolol, atenolol, alprenolol, cimetidine, clonidine, imipramine, levodopa, chlorpromazine, methyldopa, dihydroxyphenylalanine, theophylline, calcium gluconate, ketoprofen, ibuprofen, cephalexin, erythromycin, haloperidol, zomepirac, ferrous lactate, vincamine, diazepam, phenoxybenzamine, diltiazem, milrinone, capropril, mandol, quanbenz, hydrochlorothiazide, ranitidine, flurbiprofen, fenufen, fluprofen, tolmetin, alclofenac, mefenamic, flufenamic, difuinal, nimodipine, nitrendipine, nisoldipine, nicardipine, felodipine, lidoflazine, tiapamil, gallopamil, amlodipine, mioflazine, lisinolpril, enalapril, enalaprilat, captopril, ramipril, famotidine, nizatidine, sucralfate, etintidine, tetratolol, minoxidil, chlordiazepoxide, diazepam, amitriptyline, and imipramine. Further examples are proteins and peptides which include, but are not limited to, insulin, colchicine, glucagon, thyroid stimulating hormone, parathyroid and pituitary hormones, calcitonin, renin, prolactin, corticotrophin, thyrotropic hormone, follicle stimulating hormone, chorionic gonadotropin, gonadotropin releasing hormone, bovine somatotropin, porcine somatotropin, oxytocin, vasopressin, GRF, prolactin, somatostatin, lypressin, pancreozymin, luteinizing hormone, LHRH, LHRH agonists and antagonists, leuprolide, interferons, interleukins, growth hormones such as human growth hormone, bovine growth hormone and porcine growth hormone, fertility inhibitors such as the prostaglandin fertility promoters, growth factors, ~~coagultion~~ coagulation factors, human pancreas hormone releasing factor, analogs and derivatives of these compounds, and pharmaceutically acceptable salts of these compounds, or their analogs or derivatives.

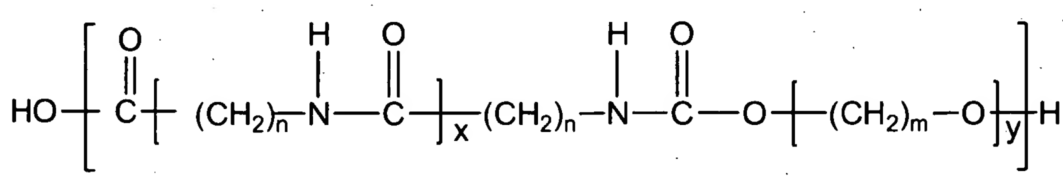
Please replace paragraph number **[00120]** with the following rewritten paragraph:

[00120] According to other embodiments of the present invention, the enclosure 71 may take different forms. For example, as described above, the delivery ~~orifice~~ port 75 may be formed in a soft impermeable material inserted into the enclosure 71. In addition, the ~~moveable~~ movable separating member 74 may be a flexible member such as a diaphragm, partition, pad, flat sheet, spheroid, or rigid metal alloy, and may be made of any number of inert materials.

Furthermore, the osmotic device 70 may function without the separating member 74, having simply an interface between the osmotic agent 78 and the beneficial agent 72.

Please replace paragraph number **[00122]** with the following rewritten paragraph:

[00122] FIG. 8 is a graph of the release rate of beneficial agent over time and compares an osmotic delivery system according to the present invention with an osmotic delivery system incorporating a conventional membrane plug, such as that illustrated in FIG. 1. As described above, the osmotic delivery system~~70~~ 70, according to the present~~invention~~ invention, includes an osmotic delivery system plug~~30~~ 30, according to the present invention. Both the prior membrane plug and the osmotic delivery system plug 30 tested in FIG. 8 were made of the same membrane material, PEBAX. The chemical structure of PEBAX is:



wherein,

$n = 5$, or 11

$m = 2$, or 4

x and y are selected according to the desired molecular weight.

Please replace paragraph number **[00123]** with the following rewritten paragraph:

[00123] As shown in FIG. 8, the osmotic delivery system 70 incorporating the prior membrane plug delivered approximately 2 µl/day of the beneficial agent from the osmotic delivery system. Comparatively, the osmotic delivery system having a membrane plug 30 according to the present invention released about 4 µl/day of beneficial agent even~~through~~ though the same semipermeable material was used for the plugs in each osmotic delivery system tested.

Please replace paragraph number **[00124]** with the following rewritten paragraph:

[00124] FIGS. 9-11 are also graphs of the release rate of beneficial agent over time and each compare osmotic delivery systems according to the present invention having membrane plugs 30 with various ~~depth~~ recesses 52.

Please replace paragraph number **[00125]** with the following rewritten paragraph:

[00125] The objectives of the experiments conducted to obtain the results depicted in FIGS. 9-11 were to evaluate (1) the influence of the depth of the interior portion 52 of the membrane plug 30 on the release rate of beneficial agent, and (2) the influence of the water uptake of membrane plug materials on the release rate. The subassembly components of the osmotic delivery systems 70 tested included: titanium enclosures 71; 80% sodium chloride osmotic agent ~~tablets~~ 78 (2x50 mg); C-flex pistons 74; silicone medical fluid (350 cs); and HDPE spiral orifice delivery ports (6 mil channel diameter). Spiral orifice delivery ports are disclosed in United States Patent Serial No. 08/595,761, the entire disclosure of which is incorporated herein by reference.

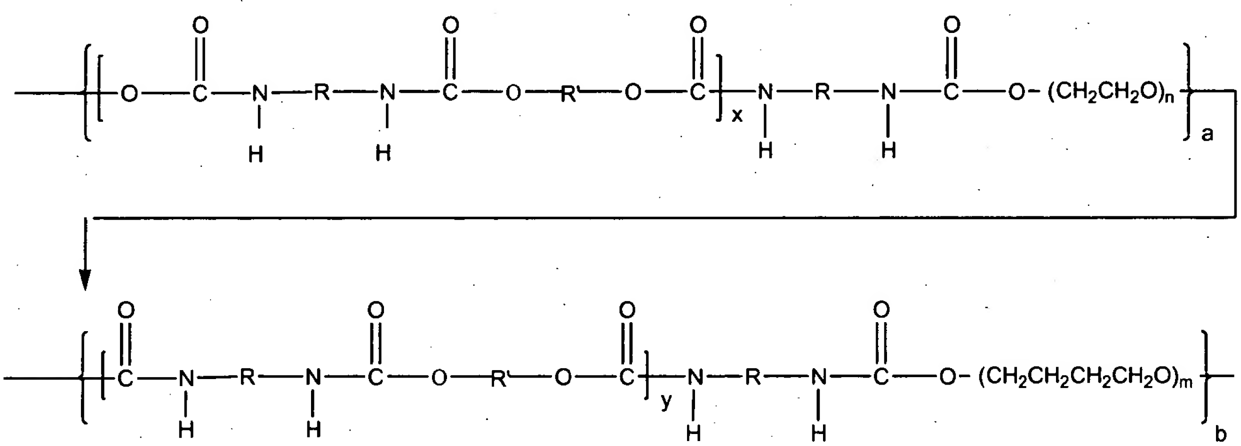
Please replace paragraph number **[00126]** with the following rewritten paragraph:

[00126] The vehicle ~~formulations~~ <u>formulation</u> of the beneficial agent used in the osmotic delivery systems tested was 2% Blue #1 in purified water (USP). The configuration of the membrane plugs 30 were: HP-60D-20b (1.5% clearance) with recess depths of 0, 59, 94 and 133 mils; HP-60D-42 (7.5% clearance) with recess depths of 0, 59, 94 and 133 mils; and HP-60D-60 (7.5% clearance) with recess depths of 0, 59, 94 and 133 mils. The inserts 60 tested in the membrane plugs 30 were made from HDPE porous ~~rod~~ <u>rods</u> with a pore size of 15 - 45 μ (available from POREX).

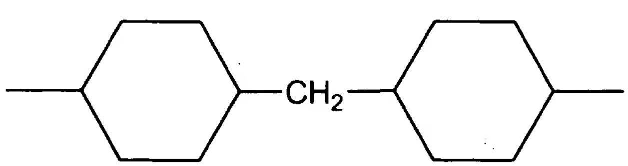
Please replace paragraph number **[00127]** with the following rewritten paragraph:

[00127] All pistons and enclosures were ~~pre-~~ <u>pre</u>lubricated. Sequentially, pistons 74 were first inserted into the enclosures 71. The enclosures were then filled with 10 μl of PEG-400 and ~~thereafter~~ <u>thereafter,</u> two osmotic ~~tablets~~ <u>agent</u> 78 <u>tablets</u> were inserted. The HDPE insert

plus 30 was presoaked in PEG-400 to eliminate any air trapped in the pores. The semipermeable bodies 32 were ultradried and the porous HDPE inserts were ~~pre-~~preinserted into the recess 52. After the osmotic delivery systems were assembled, they were then submerged in a water bath at 37°C. Beneficial agent release rate measurements were determined three times during the first week after insertion, two times during the second week, and weekly thereafter. The depth of the recess 52 and corresponding length of the insert 60 were either 0, 59, 94, or 131 mils, as measured from the insert ends 56 of the membrane plugs 30. The diameter of the inserts 60 and recesses 52 for all tests ~~were~~ was kept constant and ~~were~~ was approximately 2.0 mm. The diameter and thickness or length (measured from end to end) of the semipermeable bodies 32 were also kept constant and were approximately 2.99 mm (diameter) and 150 mils (length). The specific membrane material used in the experiments was ~~tecophilic~~ Tecophilic polyurethane (~~TECOPHILIC~~TECOPHILIC®, commercially available from THERMEDIC~~S~~) having either 18%, ~~33 %~~ 33% or 49% water uptake. The chemical structure of ~~tecophilic~~ Tecophilic polyurethane is understood to be:



R:



R': $-CH_2CH_2CH_2CH_2-$

Please replace paragraph number **[00131]** with the following rewritten paragraph:

[00131] The test results are illustrated in FIGS. 9-11. As described above, FIGS. 9-11 illustrate the release rate over time for osmotic delivery systems including ~~TECOPHILIC~~ TECOPHILIC® membrane plugs 30 having constant water uptake and different depth recesses 52. As illustrated, by increasing the depth of recess 52 (controlling the effective thickness L of the membrane plugs), the release rate of the beneficial agent increases. Thus, the liquid permeation rate through the membrane plugs 30 according to the present invention may be controlled even though the permeability coefficient for the membrane material is constant. In sum, many different membrane plugs 30 (having different effective thicknesses L and different permeation rates) may be formed from one membrane material. This is especially advantageous in that delivery system ~~plugs~~ plugs, according to the present ~~invention~~ invention, may be manufactured from one semipermeable ~~material~~ material, which has been tested and shown to be ~~biocompatible~~ biocompatible, ~~does,~~ does not have high uptake characteristics, does not tend to dislodge from the delivery system enclosure, and does not permit items within the osmotic delivery system to escape or leak to the environment of use.

Please replace paragraph number **[00132]** with the following rewritten paragraph:

[00132] FIGS. 13-20, 25, and 28 illustrate alternative embodiments of osmotic delivery systems according to the present invention. The foregoing and following discussion of the benefits and functions of the osmotic delivery system 70 also applies to the osmotic delivery systems 270, 370, 470, 570, 670, 770, 870, 970, 1070, and 2070. Thus, the osmotic delivery ~~system~~ systems illustrated in FIGS. 13-20, ~~and 25~~ 25, and 28 have been assigned corresponding reference numbers as the osmotic delivery system 70, increased by hundreds. The osmotic delivery systems illustrated in FIGS. 13-20, 25, and 28 also include many additional features and inherent functions, as described further below.

Please replace paragraph number **[00133]** with the following rewritten paragraph:

[00133] FIG. 13 illustrates one embodiment of an osmotic delivery device or system 270. As illustrated in FIG. 13, the osmotic delivery system 270 includes an elongated

substantially cylindrical enclosure 271 having an opening through which a semipermeable body assembly 230 has been inserted. The semipermeable body assembly 230 includes a semipermeable body 232 and a liquid impermeable sleeve 280. The end of the enclosure 271 opposite the opening through which the semipermeable body assembly 230 has been inserted has one or more delivery ports 275 for delivering a beneficial agent 272 from the osmotic delivery system 270. The elongated enclosure 271 is formed of a material which is sufficiently rigid to withstand expansion of an osmotic agent 278 without changing shape or size. The elongated enclosure 271 is preferably substantially impermeable to fluids in the environment of use as well as to ingredients contained within the osmotic delivery ~~device~~ system 270 such that the migration of such materials into or out of the device through the impermeable material of the enclosure is so low as to have substantially no adverse impact on the function of the osmotic delivery device.

Please replace paragraph number **[00134]** with the following rewritten paragraph:

[00134] Within the enclosure 271 is the beneficial agent 272 to be delivered, and an optional piston 274. The osmotic agent 278 within the enclosure 271 is separated from the beneficial agent 272 by the piston 274. The enclosure 271 receives the osmotic agent 278, which in the embodiment of the present invention depicted in FIG. 13 is one or more osmotic tablets. The osmotic ~~tablet~~ agent 278, in the form of a tablet, drives the osmotic flow of the osmotic delivery ~~device~~ system 270.

Please replace paragraph number **[00135]** with the following rewritten paragraph:

[00135] As illustrated in FIG. 13, the osmotic delivery ~~device~~ system 270 includes an osmotic delivery system semipermeable body assembly 230 having the semipermeable body 232 and the liquid impermeable sleeve 280 which have been inserted into the cylindrical opening of the enclosure 271. The osmotic agent 278 is directly adjacent to or touching the semipermeable body 232. The semipermeable body 232 allows liquid to pass from an environment of use into the enclosure 271 to cause the osmotic agent 278 to swell. However, as described earlier, the material forming the semipermeable body 232 is largely impermeable to the materials within the enclosure and other ingredients within the environment of use. The

semipermeable body 232 and the liquid impermeable sleeve 280 together define the osmotic delivery system semipermeable body assembly 230 that controls the delivery rate of the beneficial agent 272 from the osmotic delivery system 270. The configuration of the semipermeable body 232 and the liquid impermeable sleeve 280 dictates the liquid permeation rate through the semipermeable body 252, which generally controls the delivery rate of the beneficial agent 272 from the osmotic delivery system 270.

Please replace paragraph number **[00136]** with the following rewritten paragraph:

[00136] The semipermeable body 232 is cylindrically shaped, and the outer or exterior cylindrical surface 238 of the semipermeable body 232 touches or contacts the sleeve 280. The liquid impermeable sleeve 280 is tubular or barrel shaped, although it may be shaped otherwise and still be within the confines of the present invention. For example, the liquid impermeable sleeve 280 may be thimble-shaped, V-shaped, or C-shaped. The interior cylindrical surface of the liquid impermeable sleeve 280 abuts against the exterior cylindrical surface 238 of the semipermeable body 232. Thus, the liquid impermeable sleeve 280 forms a cylindrical tube surrounding the semipermeable body 232. In the embodiment of the present invention illustrated in FIG. 13, the liquid impermeable sleeve 280 is the same length as the semipermeable body 232 in the longitudinal direction of the semipermeable body, and the entire ~~cylindrical~~ exterior cylindrical surface 238 of the semipermeable body abuts against the entire interior surface of the sleeve 280.

Please replace paragraph number **[00140]** with the following rewritten paragraph:

[00140] Because the liquid impermeable sleeve 280 abuts against or contacts the entire ~~cylindrical~~ exterior cylindrical surface 238 of the semipermeable body 232, the ~~cylindrical~~ exterior cylindrical surface 238 of the semipermeable body is not immediately exposed to liquid when the osmotic delivery system 270 is located in the liquid environment of use. The liquid impermeable sleeve 280 may be fixed to the exterior cylindrical surface 238 of the semipermeable body 232 by an interference fit, an adhesive, or other means for attaching the liquid impermeable sleeve to the semipermeable body. The liquid impermeable sleeve 280 acts

as a barrier or seal to prevent liquid from the environment of use from immediately and directly contacting the exterior cylindrical surface 238 of the semipermeable body 232 when the osmotic delivery system 270 is first exposed to liquid from the environment of use.

Please replace paragraph number **[00141]** with the following rewritten paragraph:

[00141] The liquid impermeable sleeve 280 is separate and distinct from the enclosure 271 (it is not integral with the enclosure), and surrounds only a portion of the entire peripheral surface (the ~~cylindrical~~ exterior cylindrical surface 238 and end faces) of the semipermeable body 232 such that this surrounded portion of the peripheral surface is not immediately exposed to liquid when the osmotic delivery system is located in a liquid environment of use. As illustrated in FIG. 13, the liquid impermeable sleeve surrounds only the ~~cylindrical~~ exterior cylindrical surface 238 of the semipermeable body 232 such that the ~~cylindrical~~ exterior cylindrical surface 238 is not immediately exposed to liquid when the osmotic delivery ~~system~~ system 270 is located in a liquid environment of use. When the osmotic delivery system 270 is inserted into a liquid environment of use, liquid does not immediately contact the entire ~~cylindrical~~ exterior cylindrical surface 238 of the semipermeable body because it cannot traverse through the liquid impermeable sleeve 280 or immediately travel along the interior surface of the sleeve. Of course, after the permeation liquid has thoroughly soaked the semipermeable body 232, the entire exterior cylindrical surface 238 of the semipermeable body 232 will have contacted the liquid, but this will not occur immediately after the osmotic delivery system is inserted in the liquid environment of use. The liquid from the environment of use will only travel along the interior surface of the sleeve after the liquid has entirely permeated through the semipermeable body 232.

Please replace paragraph number **[00142]** with the following rewritten paragraph:

[00142] Because the liquid impermeable sleeve 280 does not abut against the entire peripheral surface of the semipermeable body 232, the semipermeable body 232 includes an exposure or liquid contact surface 248 defined by an area of the peripheral surface of the semipermeable body that is not in contact with or surrounded by the liquid impermeable

sleeve 280. Thus, the exposure surface 248 is immediately exposed to liquids when the osmotic delivery system 270 is located in the liquid environment of use, while the outer or exterior cylindrical surface 238 is not immediately exposed to liquid when the osmotic delivery system is located in the liquid environment of use because the liquid impermeable sleeve 280 prevents the liquid from immediately contacting any surface of the semipermeable body 232 it is abutting. In other words, the permeation liquid may only travel through the semipermeable body 232 by first ~~contracting~~ contacting the liquid contact surface 248, not the ~~cylindrical outer~~ exterior cylindrical surface 238. Because the embodiment of the present invention illustrated in FIG. 13 includes a tubular liquid impermeable sleeve 280, the exposure surface 248 only includes that portion of the semipermeable body 232 that is incident to the exterior cylindrical surface 238. The exposure surface 248 is substantially perpendicular to the exterior cylindrical surface 238.

Please replace paragraph number **[00143]** with the following rewritten paragraph:

[00143] As described earlier, the beneficial delivery rate dMt/dt through a semipermeable body may be approximated by the following formula:

$$dMt/dt = dV/dt \bullet C = \{P\ A\ \Delta\pi\ /L\} \bullet C$$

Please replace paragraph number **[00144]** with the following rewritten paragraph:

[00144] In the embodiments of the present invention illustrated in FIGS. 13-20, the liquid permeation rate through the semipermeable bodies 232, 332, 432, 532, 632, 732, 832, ~~(932~~ 932, 932′, and ~~932″)~~ 932″ may be changed according to the above formula by varying the surface area ~~of each~~ of the semipermeable body that is exposed to liquid and/or the thickness of each of the semipermeable bodies 232, 332, 432, 532, 632, 732, 832, ~~(932~~ 932, 932′, ~~932″)~~ 932″.

Please replace paragraph number **[00146]** with the following rewritten paragraph:

[00146] As described above in reference to the osmotic delivery system 70, the liquid permeation rate through the semipermeable body 32 may be controlled by varying the effective thickness L of the semipermeable body 32. In the embodiment of the present invention

illustrated in FIG. 13, the liquid permeation rate through the semipermeable body 232 may be controlled or changed by varying the thickness of the semipermeable body 232. For example, by decreasing the thickness of the semipermeable body 232, the liquid permeation rate through the semipermeable body 232 will increase to correspondingly increase a delivery rate of the beneficial agent 272 from the osmotic delivery system 270. This may be achieved by first forming, such as by injection molding, the semipermeable body 232 from a semipermeable material having a predetermined liquid permeability coefficient. The semipermeable body 232 may also be formed with a ~~set~~ set, or ~~predetermined~~ predetermined, longitudinal length or thickness that corresponds to a predetermined or desired liquid permeation rate. The semipermeable body 232 may also be formed with a predetermined diameter that defines a surface area of the liquid contact surface 248 and also corresponds to a predetermined or desired liquid permeation rate.

Please replace paragraph number **[00148]** with the following rewritten paragraph:

[00148] The semipermeable body 232 and the sleeve 280 can be molded together such that the two items are "preassembled" and form the osmotic delivery system semipermeable assembly 230. For example, the liquid impermeable sleeve may ~~be~~ be a laminate outer coating on the semipermeable body 232. The semipermeable body 232 can also be inserted into the sleeve 280 after it has been formed, in which case the sleeve 280 will matingly receive the semipermeable body 232. Accordingly, it should be realized that the length of the sleeve 280 and the semipermeable body 232 may be decreased separately and then assembled to form the semipermeable body assembly 230. Alternatively, the length of the semipermeable body assembly 230 (semipermeable body 232 and liquid impermeable sleeve 280) can be decreased by simultaneously decreasing the length of the semipermeable body and the liquid impermeable sleeve 280. Any variety of techniques may be used to decrease the thickness of the semipermeable body 232 and sleeve 280, including shearing, cutting, tearing, laser slicing, grinding, etc.

Please replace paragraph number **[00151]** with the following rewritten paragraph:

[00151] The liquid permeation rate through the semipermeable body 232 may also be controlled or varied by removing a portion of the liquid impermeable sleeve 280 from the exterior cylindrical surface 238 of the semipermeable body to increase the amount of surface area of the semipermeable body 232 that is immediately exposed to liquids when the osmotic delivery system 270 is located in its environment of use. This may be achieved by cutting through the liquid impermeable sleeve 280, but not the semipermeable body 232, and then removing the portion of the sleeve directly adjacent to the cut. Thus, the exposure surface will then include the end surface and a portion of the ~~cylindrical~~ exterior cylindrical surface 238. Increasing the amount of exposure surface area will increase the liquid permeation rate through the semipermeable body 232.

Please replace paragraph number **[00152]** with the following rewritten paragraph:

[00152] In the above described manner, the liquid permeation rate through the semipermeable membrane 232 can be controlled. Although not illustrated, the ~~semipermeably~~ semipermeable body assembly 230 may also be configured with a recess and insert like the plug 30 illustrated in FIG. 7. This is further advantageous because a low liquid uptake membrane material can be used for the semipermeable body 232, while still permitting the liquid permeation rate to be controlled.

Please replace paragraph number **[00153]** with the following rewritten paragraph:

[00153] FIG. 14 illustrates another embodiment of an osmotic delivery ~~device or~~ system 370. As illustrated in FIG. 14, the osmotic delivery system 370 includes an elongated cylindrical enclosure 371 having an opening through which a semipermeable body assembly 330 has been inserted. The semipermeable body assembly 330 includes the semipermeable body 332 and the liquid impermeable sleeve 380, similar to the semipermeable body 232 and liquid impermeable sleeve 280 illustrated in FIG. 13. The enclosure 371 receives the osmotic agent 378, which drives the osmotic flow of the osmotic delivery ~~device~~ system 370.

Please replace paragraph number **[00154]** with the following rewritten paragraph:

[00154] As illustrated in FIG. 14, only the semipermeable body 332 has been inserted into~~ to the~~ the opening of the enclosure 371. The liquid impermeable sleeve 380 is not located within the enclosure 371 because it has not been inserted in the opening of the enclosure. The osmotic agent 378 is directly adjacent~~ to~~ to, or abuts~~ against~~ against, the semipermeable body 332. The semipermeable body 332 allows liquid to pass from an environment of use into the enclosure 371 to cause the osmotic agent 378 to swell. The semipermeable body 332 and the liquid impermeable sleeve 380 together define an osmotic delivery system semipermeable body assembly 330 that controls a delivery rate of beneficial agent from the osmotic delivery system 370. The configuration of the semipermeable body 332 and the liquid impermeable sleeve 380 dictates the liquid permeation rate through the semipermeable body, which generally controls the delivery rate of the beneficial agent (not illustrated) from the osmotic delivery system 370.

Please replace paragraph number **[00155]** with the following rewritten paragraph:

[00155] The semipermeable body 332 is~~ cylindrical~~ cylindrically shaped, like the semipermeable body 232 illustrated in FIG. 13, and is sized such that it is matingly received by an opening in the enclosure 371. As illustrated in FIG. 14, the semipermeable body 332 includes a plug end 333 having a series of ridges or ribs 334 which form a seal with the interior surface of the enclosure 371. However, contrary to the osmotic delivery system illustrated in FIG. 13, the liquid impermeable sleeve 380 is not inserted into the enclosure 371. The liquid impermeable sleeve 380 is located~~ external~~ outside of the enclosure 371. The liquid impermeable sleeve 380 abuts against the exterior surface 338 of the semipermeable body 332 such that the cylindrical exterior surface 338 of the semipermeable~~ body~~ body 332 is not immediately exposed to liquid when the osmotic delivery system 370 is located in the liquid environment of use. Liquid from the environment of use is also not allowed to substantially penetrate the joint between the sleeve 380 and the enclosure 371. Because the liquid impermeable sleeve 380 is not inserted into the enclosure 371, the semipermeable body 332 alone operates like a cork or stopper when it is

inserted into the enclosure 371 of the osmotic delivery system 370, similar to the plug 30 illustrated in FIG. 7.

Please replace paragraph number **[00156]** with the following rewritten paragraph:

[00156] Like the liquid impermeable sleeve 280, the liquid impermeable sleeve 380 is separate from the enclosure 271, and surrounds only a portion of the entire peripheral surface of the semipermeable body 332 such that a portion of the peripheral surface is not immediately exposed to liquid when the osmotic delivery system is located in the liquid environment of use. Because the liquid impermeable sleeve 380 does not abut against the entire peripheral surface of the semipermeable body ~~323~~ 332, the semipermeable body includes an exposure or liquid contact surface 348 defined by an area of the peripheral surface that is not surrounded by the liquid impermeable sleeve 80 and is located ~~external~~ outside of the enclosure 371. The exposure surface 348 is immediately exposed to liquids when the osmotic delivery system 370 is located in the liquid environment of use.

Please replace paragraph number **[00157]** with the following rewritten paragraph:

[00157] The liquid permeation rate through the semipermeable body 332 of the osmotic delivery system 370 may be controlled or changed by varying the thickness of the semipermeable body 332. For example, the liquid permeation rate through the semipermeable body 332 may be changed to increase a delivery rate of the beneficial agent from the osmotic delivery system. The liquid permeation rate through the semipermeable body 332 may be increased by decreasing the thickness of the semipermeable body by, for example, cutting the semipermeable body. The semipermeable body 332 may be cut before or after it has been inserted into the enclosure 371. When cutting the semipermeable body 332, the liquid impermeable sleeve 380 may also be cut. That is, both the liquid impermeable sleeve 380 and the semipermeable body 332 may be cut in one action to decrease the thickness of both the liquid impermeable sleeve and the semipermeable body 332 in the longitudinal direction of the semipermeable body, i.e., parallel with the cylindrical exterior surface 338 of the semipermeable body 332.

Please replace paragraph number **[00158]** with the following rewritten paragraph:

[00158] The liquid permeation rate through the semipermeable body 332 may also be controlled by increasing the amount of surface area of the semipermeable body that is immediately exposed to liquids when the osmotic delivery system 370 is placed in its environment of use. The liquid permeation rate may be increased by removing a portion of the liquid impermeable sleeve 380 such that the amount of exposure surface 348 that is exposed to liquids is increased.

Please replace paragraph number **[00159]** with the following rewritten paragraph:

[00159] The liquid impermeable sleeve 380 can be fixed to the semipermeable body 332 by an adhesive or other means that prevent the sleeve from moving relative to the semipermeable body 332. Alternatively, the sleeve 332 can be ~~moveable~~ movable relative to the body 332, although still contacting the cylindrical exterior surface 338 of the semipermeable ~~body~~ body 332.

Please replace paragraph number **[00160]** with the following rewritten paragraph:

[00160] FIG. 15 illustrates another embodiment of an osmotic delivery system 470 according to the present invention. The osmotic delivery system 470 includes an enclosure 471 having an opening through which a semipermeable body 432 of a semipermeable body assembly 430 has been inserted. The semipermeable body 432 is similar to the semipermeable body 332 illustrated in FIG. 14 as the semipermeable body 432 includes a plug end 433 that has been inserted into the enclosure 471. Thus, only a portion of the semipermeable body 432 has been inserted into the enclosure 471. The semipermeable body 432 allows liquid to pass from an environment of use into the enclosure 471 to cause the osmotic agent 478 to swell and move the piston 474. The semipermeable body 432 and the liquid impermeable sleeve 480 together define the semipermeable body assembly 430 that controls a delivery rate of beneficial agent from the osmotic delivery system 470. The configuration of the semipermeable body 432 and the liquid impermeable sleeve 480 dictates the liquid permeation rate through the semipermeable ~~body~~

body 432, which generally controls the delivery rate of the beneficial agent from the osmotic delivery system 470.

Please replace paragraph number **[00161]** with the following rewritten paragraph:

[00161] The liquid impermeable sleeve 480 is tubular, and abuts against the cylindrical exterior surface 438 of the cylindrical semipermeable body 432. In the embodiment of the present invention illustrated in FIG. 15, the liquid impermeable sleeve 480 is not inserted within the enclosure 471, and is thus located ~~external~~ outside of the enclosure. The liquid impermeable sleeve 480 is fixedly attached to the exterior surface of the enclosure 471 as well as the exterior surface of the semipermeable body 432. The liquid impermeable sleeve 480 is fixedly attached to the semipermeable body 432 such that the liquid impermeable sleeve and the semipermeable body are not movable with respect to each other. The liquid impermeable sleeve 480 may be fixed to the semipermeable body 432 by an adhesive, weld, bonding agent or other similar device for securing or fastening the sleeve to the body.

Please replace paragraph number **[00162]** with the following rewritten paragraph:

[00162] The liquid impermeable sleeve 480 also forms a seal between the enclosure 471 and the sleeve 480 when the liquid impermeable sleeve 480 is positioned over the enclosure 471 and is affixed to the exterior surface of the enclosure. Thus, the liquid impermeable sleeve 480 is also not movable relative to the enclosure 471. Because the liquid impermeable sleeve 480 forms a seal or a watertight joint with the enclosure ~~470~~ 471, the semipermeable body 432 need not include the plug end 433. In such an embodiment, the semipermeable body 432 is located entirely ~~external~~ outside of the enclosure 471, and the seal between the liquid impermeable sleeve 480 and the enclosure 471 prevents liquid and other substances in the environment of use, besides the permeation liquid, from entering the osmotic delivery system 470 while also preventing materials from the inside of the delivery system from leaking or escaping to the environment of use.

Please replace paragraph number **[00163]** with the following rewritten paragraph:

[00163] The liquid permeation rate through the semipermeable body 432 may be increased by changing the thickness of the semipermeable body 432 and thus the liquid permeation rate through the semipermeable body, similar to the embodiments illustrated in FIGS. 13 and 14. For instance, the semipermeable body 432 may be cut to increase the liquid permeation rate through the semipermeable body.

Please replace paragraph number **[00164]** with the following rewritten paragraph:

[00164] FIG. 16 illustrates another embodiment of an osmotic delivery ~~device or~~ system 570. As illustrated in FIG. 16, the osmotic delivery system 570 includes an elongated cylindrical enclosure 571 having an opening through which a semipermeable body 532 has been inserted. The semipermeable body 532 is a cylindrical plug of semipermeable material having a series of ~~rigid~~ ridges or ribs to help effect a seal between the semipermeable ~~body~~ body 532 and the interior surface of the liquid impermeable enclosure 571. The enclosure 571 also receives the osmotic agent 578, which drives the osmotic flow of the osmotic delivery ~~device~~ system 570 by moving the piston 574.

Please replace paragraph number **[00165]** with the following rewritten paragraph:

[00165] The semipermeable body 532 is not surrounded by a liquid impermeable sleeve that is separate and distinct from the enclosure 571. The semipermeable body 532 is only surrounded by the enclosure 571, similar to the semipermeable body 32 shown in FIG. 7. However, the enclosure 571 includes a plurality of grooves, channels, furrows, recesses or indentations 581 which define predetermined cutting locations by which an administrator can decrease the length of the enclosure 571 and the thickness of the semipermeable body 532. That is, the semipermeable body 532 surrounded by the enclosure 571 may be cut to increase the liquid permeation rate through the semipermeable body, i.e., the "effective thickness" L of the semipermeable body 532 is decreased. In this manner, the liquid permeation rate through the semipermeable body 532 may be varied to control the beneficial agent delivery rate from the osmotic delivery system 570.

Please replace paragraph number **[00167]** with the following rewritten paragraph:

[00167] FIG. 17 illustrates another embodiment of an osmotic delivery system 670 according to the present invention. As illustrated in FIG. 17, the osmotic delivery system 670 includes an elongated cylindrical enclosure 671. The osmotic delivery system 670 includes the semipermeable body assembly 630 having the semipermeable body 632 and liquid impermeable sleeve 680. As illustrated in FIG. 17, the semipermeable body 632 and the liquid impermeable sleeve 680 are both ~~external~~ outside of the enclosure 671. The semipermeable body 632 is not positioned within the enclosure 671, and is larger than the opening into the enclosure 671 such ~~that~~ that it may not be easily inserted into the enclosure. However, the osmotic delivery system 670 could be configured to receive a portion of the semipermeable body 632, such as illustrated in FIGS. 14 and 15. The enclosure 671 receives the osmotic agent 678 and the movable piston 674 and the osmotic agent 678 drives the osmotic flow of the osmotic delivery device 670.

Please replace paragraph number **[00168]** with the following rewritten paragraph:

[00168] As illustrated in FIG. 17, the semipermeable body 632 is located within the liquid impermeable sleeve 680 and the ~~sleeve~~ sleeve 680 is longer than the semipermeable ~~body~~ body 632. The liquid impermeable sleeve 680 is threaded onto the enclosure 671 via the threads 682. The liquid impermeable sleeve 680 may include threads that engage the exterior surface of the enclosure 671, the enclosure may include threads that engage the interior surface of the liquid impermeable sleeve, or both the liquid impermeable sleeve and the exterior surface of the enclosure may include threads that matingly engage each other. Because the sleeve 680 is threadable onto and off of the enclosure 671, the liquid impermeable sleeve 680 is rotatable with respect to the enclosure 671. Thus, the liquid impermeable sleeve 680 may be moved linearly with respect to the enclosure 671 by rotating the sleeve with respect to the enclosure about the longitudinal axis of the enclosure via the threads 682. The liquid impermeable sleeve 680 may be moved longitudinally along the longitudinal axis of the enclosure 671, i.e., along an axis parallel with the cylindrical wall of the enclosure, by rotating the sleeve on the threads 682.

Please replace paragraph number **[00170]** with the following rewritten paragraph:

[00170] The semipermeable body 632 is positioned within the liquid impermeable sleeve 680 such that the liquid impermeable sleeve may move relative to the semipermeable body 632. For example, the liquid impermeable sleeve 680 may receive the semipermeable body 632 and an interference fit manner sufficiently tight to retain the semipermeable ~~body~~ <u>body 632</u> within the liquid impermeable sleeve, while permitting the liquid impermeable sleeve 680 to slidingly move relative to the semipermeable membrane when the liquid impermeable sleeve is threaded onto the enclosure 671. However, the portion of the liquid impermeable sleeve 680 that abuts against the cylindrical exterior surface of the semipermeable body 632 is not immediately exposed to liquid when the osmotic delivery system 670 is located in a liquid environment of use. When the liquid impermeable sleeve 680 is threaded onto the enclosure 671, the exposure surface 648 will include more than the flat surface of the semipermeable body that is perpendicular to the liquid impermeable sleeve 680. For example, as the liquid impermeable sleeve 680 is threaded onto the enclosure 671 such that it moves toward the enclosure 671, a portion of the cylindrical exterior surface 638 of the semipermeable body 632 may be exposed to increase the liquid permeation rate through the semipermeable body.

Please replace paragraph number **[00172]** with the following rewritten paragraph:

[00172] As illustrated in FIG. 18, the osmotic delivery system 770 includes an elongated substantially cylindrical enclosure 771 having an ~~opining~~ <u>opening</u> through which a semipermeable body 732 has been inserted. The semipermeable body 732 is part of a semipermeable body assembly 730 that includes the liquid impermeable sleeve 780. Within the enclosure 771 of the osmotic delivery system 770 is the beneficial agent 772 to be delivered, and ~~amovable~~ <u>a movable</u> piston 774. The osmotic agent 778 within the enclosure 771 is separated from the beneficial ~~agent~~ <u>agent 772</u> by the movable piston 774. The enclosure 771 receives the osmotic agent 778, which drives the osmotic flow of the osmotic delivery system 770.

Please replace paragraph number **[00175]** with the following rewritten paragraph:

[00175] As illustrated in FIG. 18, the semipermeable body 732 is surrounded by the tubular liquid impermeable sleeve 780. The interior surface of the liquid impermeable sleeve 780 abuts against the cylindrical surface 738 of the semipermeable body 732 and the respective surfaces are ~~moveable~~ movable relative to each other such that the interior surface of the liquid impermeable sleeve slides relative to the exterior surface of the semipermeable body 732. As in the previous embodiments of the present invention, the liquid impermeable sleeve 780 abuts against the exterior surface of the semipermeable body 732 such that the surface area of the semipermeable body against which the liquid impermeable sleeve abuts is not immediately exposed to liquid when the osmotic delivery system is located in the liquid environment of use.

Please replace paragraph number **[00176]** with the following rewritten paragraph:

[00176] The liquid impermeable ~~sleeves~~ sleeve 780 is movable relative to the semipermeable body 732, as well as the enclosure 771 of the osmotic delivery system 770. For example, the liquid impermeable sleeve 780 is movable from the position Y to the position Y′ with respect to the semipermeable body 732 along the longitudinal direction of the enclosure 771. In this manner, the amount of surface area of exposure surface 748 that is immediately exposed to liquids when the osmotic delivery system 770 is located in its environment of use may be increased. The liquid permeation rate through the semipermeable body 732 may be controlled by increasing the amount of surface area of the semipermeable body 732 that is exposed to liquids when the osmotic delivery system is placed in its environment of use. An administrator may move or slide the liquid impermeable sleeve 780 upward or downward relative to the enclosure 771 and the semipermeable body 732 to vary the liquid permeation rate through the semipermeable body 732.

Please replace paragraph number **[00177]** with the following rewritten paragraph:

[00177] In the embodiment of the present invention illustrated in FIG. 18, the liquid impermeable sleeve 780 is fitted to the enclosure 771 via a tight interference fit. The

liquid impermeable sleeve 780 matingly engages the exterior surface of the enclosure 771 such that it may slide with respect to the exterior surface of the enclosure. Although the liquid impermeable sleeve 780 is fitted to the enclosure 771 via an interference fit, the liquid impermeable sleeve may also be movably fitted or movably attached to the enclosure 771 via other means. For example, the liquid impermeable sleeve 780 may be movably attached to the enclosure 771 through grooves, threads, or other similar devices. The exterior surface of the enclosure 771, the interior surface of the sleeve 780, or both the exterior surface of the enclosure and interim surface of the sleeve may include grooves, ridges, or lips to assist and control relative movement between the liquid impermeable ~~780~~ sleeve 780 and the enclosure 771.

Please replace paragraph number **[00178]** with the following rewritten paragraph:

[00178] The semipermeable body 732 may be inserted into the opening of the enclosure 771, ~~and~~ and, thereafter, the liquid impermeable sleeve 780 may be slid over the semipermeable body 732 and the enclosure 771 to a desired position that exposes an amount of exposure surface 748 that corresponds to a desired liquid permeation rate though the semipermeable body 732. Alternatively, the sleeve 780 may be slid over the semipermeable body 732 to a desired position that exposes an amount of exposure surface 748 that corresponds to a desired liquid permeation rate through the semipermeable body 732 before the semipermeable body assembly 730 is positioned in the enclosure 771. After the liquid impermeable sleeve 780 has been positioned to its desired location, an adhesive can be used to bond the liquid impermeable sleeve to the enclosure 771, such that it is ~~not~~ no longer movable with respect to the enclosure 771 and the semipermeable body 732.

Please replace paragraph number **[00179]** with the following rewritten paragraph:

[00179] FIG. 19 illustrates another embodiment of an osmotic delivery system 870 according to the present invention. As illustrated in FIG. 19, the semipermeable body assembly 830 includes a liquid impermeable sleeve 880 and a semipermeable body 832. The semipermeable body 832 has been inserted into the enclosure 871 of the osmotic delivery system 870. The semipermeable body 832 allows liquid to pass from an environment of use into

the enclosure 871 to cause the osmotic agent 878 to swell and drive the piston 874. The osmotic ~~tablet~~ agent 878 thus drives the osmotic flow of the osmotic delivery ~~device~~ system 870. As illustrated in FIG. 19, the liquid impermeable sleeve 880 includes threads 882 on its interior surface. The liquid impermeable sleeve 880 is configured similar to a pipe or conduit that has threads on its interior surface. The threads 882 extend along the center axis of the liquid impermeable sleeve 880 such that the entire interior surface of the tubular sleeve includes the threads 882. Thus, the liquid impermeable sleeve 880 may be threaded onto the semipermeable body 832 via the threads 882. A portion of the semipermeable body 832 extends from the enclosure 871 such that the liquid impermeable sleeve 880 may be threaded onto the semipermeable body 832. The liquid impermeable sleeve 880 is separate from the enclosure 871 and abuts against or surrounds only a portion of the entire peripheral surface of the semipermeable body 832 such that at least a portion of the peripheral surface of the semipermeable body is not immediately exposed to liquid when the osmotic delivery system is located in a liquid environment of use.

Please replace paragraph number **[00180]** with the following rewritten paragraph:

[00180] The liquid permeation rate through the semipermeable body 832 may be controlled by increasing the amount of surface area of the semipermeable body that is immediately exposed to liquids when the osmotic delivery system 870 is placed in its environment of use. For example, the liquid permeation rate may be increased by partially unthreading or partially removing the liquid impermeable sleeve 880 from the portion of the semipermeable body 832 that extends from the enclosure 871. That is, the liquid permeation rate may be increased by increasing the ~~exposure~~ exposed surface area of the semipermeable membrane body 832 that is immediately exposed to liquids when the osmotic delivery system is located in its environment of use. An administrator may partially unthread the liquid impermeable sleeve 880 from the semipermeable body 832 to increase the area of the exposure surface ~~area~~ 848. As illustrated in FIG. 19, by partially unthreading the sleeve 880, the liquid contact surface or exposure surface 848 will include a portion of the cylindrical exterior surface of the semipermeable body 832 as well as the flat end surface of the semipermeable body 832

that is perpendicular to the cylindrical exterior surface of the semipermeable body. However, because the end surface is always exposed to liquids when the osmotic delivery system 870 is located in a liquid environment of use, the liquid permeation rate through the semipermeable body 832 is increased by increasing the amount of the cylindrical surface area of the semipermeable body that is immediately exposed to liquids when the osmotic delivery system 870 is located in its environment of use.

Please replace paragraph number **[00181]** with the following rewritten paragraph:

[00181] The liquid impermeable sleeve 880 can also be threaded onto the semipermeable body 832 to decrease the amount of cylindrical surface area of the semipermeable body that is immediately exposed to liquids when the osmotic delivery system is located in its environment of use. The liquid permeation rate through the semipermeable body 832 may be decreased by threading the liquid impermeable sleeve 880 onto the semipermeable body 832 to decrease an amount of cylindrical surface area that is immediately exposed to liquid when the osmotic delivery system is located in its environment of use. Although the liquid impermeable sleeve includes the threads 882, alternative means for fastening the liquid impermeable sleeve 880 to the semipermeable body 832 are contemplated. For ~~example~~ example, the liquid impermeable sleeve 880 may fit onto the semipermeable body 832 via an interference fit. However, the sleeve 880 preferably does not overly compress the semipermeable body 832 such that the liquid permeation rate through the semipermeable body is affected.

Please replace paragraph number **[00182]** with the following rewritten paragraph:

[00182] The osmotic delivery system 870 may come assembled with the semipermeable body 832 extending from the enclosure 871, and an administrator may choose a liquid impermeable sleeve 880 that may ~~be fitted~~ fit over the semipermeable body 832 to vary the liquid permeation rate through the semipermeable body in the above-described manner. An administrator of the osmotic delivery system 870 may control the liquid permeation rate and hence the beneficial agent delivery rate from the osmotic delivery system 870 by simply varying the amount of surface area that is exposed to liquids when the osmotic delivery system is located

in its environment of use. An adhesive or other means may be used to secure the liquid impermeable sleeve 880 to the semipermeable body after it has been moved to its desired position relative to the exterior surface of the semipermeable body 832. As described above, by varying the amount of surface area that is immediately exposed to liquids when the osmotic delivery system 870 is located in its environment of use, the liquid permeation rate through the semipermeable body 832 can be varied to control the beneficial agent delivery rate from the osmotic delivery system 870. The thickness of the liquid impermeable sleeve 880 and/or the semipermeable body 832 may also be decreased to change the liquid permeation rate through the semipermeable body.

Please replace paragraph number **[00183]** with the following rewritten paragraph:

[00183] FIG. 20 illustrates another embodiment of an osmotic delivery system 970 according to the present invention. The osmotic delivery system 970 includes an elongated substantially cylindrical enclosure 971 having an opening through which an osmotic ~~tablet~~ agent ~~978~~ 978, in the form of a tablet, and a piston 974 have been inserted. The osmotic delivery system 970 includes a first semipermeable body 932, as well as an optional second semipermeable body 932′ ~~and~~ and an optional third semipermeable body 932″. The first semipermeable body 932, and optionally the second and third semipermeable bodies 932′ and 932″, respectively, are in liquid communication with the enclosure 971 such that liquids may permeate through the semipermeable bodies ~~932~~ 932′, and 932″ to the osmotic agent 978 and drive the osmotic flow of the osmotic delivery system 970. The end of the enclosure 971 opposite the opening through which the osmotic agent 978 has been inserted has one or more delivery ports 975 for delivering the beneficial agent 972 from the osmotic delivery system 970. The osmotic agent 978 within the enclosure 971 is separated from the beneficial agent 972 by the movable piston 974.

Please replace paragraph number **[00187]** with the following rewritten paragraph:

[00187] The first semipermeable body 932 and the first wall portion 980 can be molded in a single operation to define a unified structure ~~the~~ as the first semipermeable body

element~~930~~ 983. Alternatively, the first semipermeable body 932 may be inserted into a preformed opening in the first wall portion 980 to form the semipermeable body element ~~930~~ 983. A seal is located between the first semipermeable body 932 and the first wall portion 980 such that the interface is water-tight. The interior surface of the first wall portion 980 attaches to the exterior surface of the enclosure 971 such that the first semipermeable body 932, held by the first wall portion 980, is also attached to the enclosure 971.

Please replace paragraph number **[00188]** with the following rewritten paragraph:

[00188] Although the first wall portion 980 of the first semipermeable body element 983 illustrated in FIG. 20 is tubular, it may be other configurations. For example, the first wall portion 980 and first semipermeable body 932 may be rectangular and together define the shape of a rectangular adhesive bandage such as a BAND-~~AID~~AID® brand adhesive bandage. This configuration is particularly suitable for osmotic delivery systems that already include a semipermeable plug that seals the enclosure, such as that illustrated in FIG. 1. Such a semipermeable body element need not prevent materials from the exterior environment from entering the interior of the enclosure 971, as the semipermeable plug inserted in the enclosure of the osmotic delivery device already seals the enclosure from external materials, except for the permeation liquid.

Please replace paragraph number **[00192]** with the following rewritten paragraph:

[00192] The second wall portion 980′ may be affixed or attached to the exterior surface of the first wall portion ~~980′~~ 980 of the first semipermeable body element 983 via an adhesive or other means for securing or attaching the second wall portion ~~980~~ 980′ to the first wall portion 980 ~~enclosure~~ enclosure 971. For example, the second wall portion 980′ may be rigid and thread onto the first wall portion 980 or may be flexible and stretch over the first wall portion 980.

Please replace paragraph number **[00193]** with the following rewritten paragraph:

[00193] The thickness of the net semipermeable body may be further increased by positioning a third semipermeable body element 983″ on top of the first and second semipermeable body elements 983, 983' such that the third semipermeable body 932″ is adjacent and abutting the second semipermeable body 932′. By positioning the semipermeable bodies 932, 932′, 932″ in abutting relationship to one another, the semipermeable bodies are in liquid communication with each other so as to permit liquid to permeate through each of the semipermeable bodies 932, 932′, 932″ to the osmotic agent 978. For example, with an osmotic delivery system 970 that includes three abutting or layered semipermeable body elements 983, 983′, 983″, liquid from an external environment of use will first permeate through the ~~first~~ third semipermeable body 932″ to the second semipermeable body 932′ and eventually through the first semipermeable body 932 such that the osmotic agent may swell and drive the osmotic flow of the osmotic delivery system 970.

Please replace paragraph number **[00195]** with the following rewritten paragraph:

[00195] As described above, the stacked semipermeable body elements ~~933, 933′, 933″~~ 983, 983′, 983″ form layers of semipermeable bodies 932, 932′, 932″. By removing or adding layers, the liquid permeation rate through the net semipermeable body of the system 970 may be controlled or varied. When the semipermeable bodies 932, 932′, 932″ are stacked or layered as described above, the semipermeable bodies 932, 932′, 932″ are in liquid communication with the liquid impermeable enclosure 971 to permit liquid from the environment of use to permeate through all of the semipermeable bodies to the osmotic agent 978 within the enclosure 971.

Please replace paragraph number **[00197]** with the following rewritten paragraph:

[00197] Although not illustrated, the second and third semipermeable body elements 983′, 983″ may include a semipermeable body 932′, 932″ that has a greater exposure surface area than that of the first semipermeable body 932. Likewise, the thicknesses of the second and third semipermeable bodies 932′, 932″ in the axial or longitudinal direction of the

enclosure 971 may vary. Thus, the net thickness and the net exposure surface area A of the net semipermeable body of the osmotic delivery system 970 may be controlled by removing or adding semipermeable body elements 983 (983′, 983″) of different and varying configurations, i.e., having varying thicknesses and varying ~~exposed surface areas~~ exposure surfaces 948, 948′, 948″.

Please replace paragraph number **[00201]** with the following rewritten paragraph:

[00201] FIG. 21 illustrates a side view of the osmotic delivery system plug 1030. The plug 1030 is formed from a semipermeable body 1032. The semipermeable body 1032 includes a cylindrical portion 1031, and a conical portion 1033 located directly adjacent to the cylindrical portion 1031. The conical portion 1033 is in the shape of a right circular cone having a cone-shaped surface 1048, a vertex 1049, and a cone base 1041. The vertex 1049 of the cone-shaped surface 1048 is located opposite ~~from~~ the cylindrical portion 1031 and the base 1041 of the conical portion. When positioned in the enclosure of an osmotic delivery system 1070, the vertex faces away from the osmotic agent 1078. As shown in FIG. 21, the vertex 1049 is a rounded or smoothed point.

Please replace paragraph number **[00202]** with the following rewritten paragraph:

[00202] The semipermeable body 1032 includes means for sealing or ribs 1034 that extend away from the outer surface 1038 of cylindrical ~~portion~~ portion 1031 of the plug 1030. The ribs 1034 are located at the cylindrical portion 1031 of the semipermeable body 1032. The ribs 1034 are the means by which the plug 1030 operates like a cork or stopper, obstructing and plugging an opening 1079 in the enclosure 1071 of the osmotic delivery system 1070 illustrated in FIG. 25. The semipermeable body 1032 is, therefore, intended for at least partial insertion into the opening 1079 of the enclosure 1071. The ribs 1034 seal the environment of use from an inside of the enclosure 1071 to prevent liquid and other substances in the environment of use, besides the permeation liquid, from entering the osmotic delivery system 1070 while also preventing materials from the inside of the delivery system from leaking or escaping to the environment of use.

Please replace paragraph number **[00203]** with the following rewritten paragraph:

[00203] As illustrated in FIGS. 21 and 25, the cylindrical portion 1031 having the ribs 1034 is intended for at least partial insertion in an osmotic delivery system opening 1079. The plug 1030 is partially or entirely insertable into the opening 1079. Because at least a portion of the plug 1030 is in contact with the interior surface of the enclosure 1071, and has means for sealing 1034, only a portion of the entire exterior surface of the semipermeable body 1032 is immediately exposed to liquids in the environment of use. In the embodiment of the present invention illustrated in FIGS. 21-25, the cone-shaped or conical surface 1048 of the conical portion 1033 is the exposure surface or liquid contact surface, i.e., that portion of the semipermeable body which is immediately exposed to liquids when the osmotic delivery system is placed in a liquid environment of use. Thus, the cylindrical portion 1031 is not immediately exposed to liquids when the osmotic delivery system 1070 is placed in a liquid environment of use, while the conical portion 1033 is immediately exposed to liquids when the osmotic delivery system 1070 is placed in a liquid environment of use.

Please replace paragraph number **[00205]** with the following rewritten paragraph:

[00205] Additionally, it is not necessary that the osmotic delivery system plug 1030 include the cylindrical portion 1031. As illustrated in FIGS. 26 and 27, the osmotic delivery system plugs 2030, 2030′ include a semipermeable body 2032,~~ 2030′~~ <u>2032′</u> that is entirely cone-shaped.

Please replace paragraph number **[00206]** with the following rewritten paragraph:

[00206] As illustrated by FIG. 27, the conical-shaped semipermeable body 2032′ may also include ribs 2034′ on the conical exterior surface 2048′ of the body. As shown in ~~FIG~~<u>FIG.</u> 28, a plurality of the ribs 2034′ contact the interior surface of the enclosure 2071 when the semipermeable body 2032′ is inserted into the opening of the enclosure of the osmotic delivery system 2070 according to another embodiment of the present invention. The base 2041′ of the cone-shaped semipermeable body 2032, 2032′ has a diameter that is greater than the internal diameter of the opening into the enclosure through which the body is~~ to~~ <u>to be</u> inserted.

Thus, as illustrated in FIG. 28, the base 2041′ of the cone-shaped semipermeable body 2032′ deflects when the semipermeable body is inserted into the enclosure 2071.

Please replace paragraph number **[00207]** with the following rewritten paragraph:

[00207] The semipermeable bodies 2032, 2032′ illustrated in FIGS. 26-28 include a conical recess or cone-shaped hollow portion 2052, 2052′. Because the base 2041, 2041′ of the semipermeable body 2032, 2032′ deflects when it is inserted into the enclosure 2071, the shape of the conical recess 2052, 2052′ also changes. In the osmotic delivery system 2070, the semipermeable body 2032′ has only been partially inserted into the enclosure 2071. Hence, a portion of the semipermeable body extends out of the enclosure 2071. The portion of the conical exterior surface 2048′ that is not in contact with the enclosure 2071 and faces away from the osmotic agent 2078 will be immediately exposed to liquids when the osmotic delivery ~~system~~ system 2070 is located in a liquid environment of use.

Please replace paragraph number **[00208]** with the following rewritten paragraph:

[00208] As shown in FIG. 25, the osmotic delivery system plug 1030 can be located entirely within the enclosure 1071 such that the cone-shaped surface 1048 is also located entirely within the enclosure 1071. The plug 1030 may be inserted entirely through an opening 1079 of the enclosure 1071 of the osmotic delivery system 1070 because the plug 1030 does not include a stop surface or head preventing complete insertion, such as the stop surface 36 illustrated in FIG. 2. When the plug 1030 is completely inserted within the enclosure 1071 of the osmotic delivery system, the cone-shaped surface 1048 defines the liquid or exposure surface of the plug because it is immediately exposed to liquids when the an osmotic delivery system 1070 is placed in a liquid environment of use. The plug 1030 may also be partially inserted into the opening 1079 of an osmotic delivery system enclosure 1071 such that a portion of the conical liquid contact surface 1048 is ~~external~~ outside of the enclosure 1071.

Please replace paragraph number **[00210]** with the following rewritten paragraph:

[00210] As illustrated by FIG. 28, the cylindrical wall of the enclosure 2071 has two openings located opposite from each other and each configured to receive the flow moderator device 2074 and the osmotic delivery system plug 2030′. Thus, the enclosure 2071 includes a cylindrical tube having two opposing openings into the cylindrical tube. It will be appreciated that the plug 2030′, as well as the previously described osmotic delivery system plugs 30, 130, 1030, 1030′, 2030, ~~2030′~~ can be inserted through either of the openings into the interior of the enclosure 2071. For example, in assembling the osmotic delivery ~~device~~ system 2070 according to one embodiment of the present invention, the plug 2030′ is inserted "vertex first" through an opening into the enclosure 2071. Once the osmotic agent ~~tablet~~ 2078 has been formed, it is placed inside the enclosure 2071 through the same opening such that the tablet is adjacent to the plug 2030′. Then, the ~~separating member~~ flow moderator device 2074 is inserted through the same opening so that the ~~separating member~~ flow moderator device 2074 is on the side of the osmotic ~~tablet~~ agent 2078 opposite from the plug 2030′. The enclosure 2071 is then filled with the beneficial agent 2072 and the flow moderator device 2073 is placed into the same opening of the enclosure 2071 to close off and seal the osmotic delivery system 2070.

Please replace paragraph number **[00211]** with the following rewritten paragraph:

[00211] ~~FIG.~~ FIGS. 23A and 23B depict the cross-sections of semipermeable bodies 1032, 1032′ according to the present invention. The semipermeable bodies 1032, 1032′ each include a hollow interior portion or recess 1052, 1052′. In the embodiment of the present invention depicted in FIG. 23A, the recess 1052 is cylindrically shaped. The recess 1052 has a cylindrical and longitudinal interior surface 1054 which begins at an insert opening 1055 formed by the recess 1052 in the insert end 1056 of the semipermeable body 1032, and ends at a depth surface 1050 within the body 1032. Because of the cylindrical shape of the cylindrical portion 1031 of the semipermeable body 1032 and the cylindrical shape of the recess 1052, the body includes a cup-shaped region, where the "bottom of the cup" is conical and has a predetermined plug thickness t and the wall 1057 has a predetermined wall width w, similar to the plug 30 illustrated in FIG. 4B.

Please replace paragraph number **[00212]** with the following rewritten paragraph:

[00212] As shown in FIG. 23A, the predetermined wall width w is defined by the location of the outer surface 1038 relative to the interior surface 1054, and the predetermined plug thickness t is defined by the location of the depth surface 1050 relative to the conical surface 1048. Because the ~~conical~~ cone-shaped surface 1048 slopes relative to the depth surface 1050, the predetermined plug thickness t actually changes along the slope of the conical surface.

Please replace paragraph number **[00213]** with the following rewritten paragraph:

[00213] As described above in reference to the plug 30, the depth of the depth surface 1050 within the semipermeable body 1032, and the distance the interior surface 1054 is from the longitudinal center axis C (or diameter 1046 of the recess 1052) determine the size of the hollow ~~interior portion~~ recess 1052 in the interior of the semipermeable body 1032. Together, the predetermined wall width w and the predetermined plug thickness t define the effective thickness L of the semipermeable body 1032. As described above, by varying the size of the recess ~~or hollow interior portion~~ 1052, or, in other words, by varying the predetermined plug thickness t and/or the predetermined wall width w, the effective thickness L of the semipermeable body 1032 of the osmotic delivery system plug 1030 may also be varied. In this manner, the liquid permeation rate through the body 1032 can be controlled.

Please replace paragraph number **[00214]** with the following rewritten paragraph:

[00214] For instance, by decreasing the effective thickness L of the semipermeable body 1032 of the plug 30, the liquid permeation rate dV/dt through the plug may be increased. As illustrated in FIG. 23B, the effective thickness L of the semipermeable body 1032′ may be decreased by decreasing the predetermined plug thickness t′ of the semipermeable body. This is achieved by increasing the size of the recess ~~1052~~ 1052′.

Please replace paragraph number **[00215]** with the following rewritten paragraph:

[00215] FIG. 23B illustrates a preferred semipermeable body 1030′. The recess 1052′ includes a cylindrical portion and a conical portion. Hence, the recess 1052′ is in the shape of a bullet and has a volume greater than the cylindrical recess 1052. Alternatively, the recess 1052 can be entirely conical, such as the recesses 2052, 2052′ shown in FIGS. 26 and 27. The recess 1052′ generally follows the contours of the outer surface 1038 and cone-shaped surface ~~1048~~ 1048′. The distance of the depth surface 1050′ relative to the ~~conical surface~~ cone-shaped 1048′ is constant, and the distance of the outer surface 1038′ relative to the interior surface 1054′ is constant. Thus, the predetermined wall width w′ and the predetermined plug thickness t′ are approximately equal and constant. Although not illustrated, the semipermeable bodies 1030, 2030 need not include a recess or hollow portion.

Please replace paragraph number **[00216]** with the following rewritten paragraph:

[00216] FIGS. 24 and 25 illustrate inserts 1060, 1060′ that can be included in an exemplary osmotic delivery plug 1030 or osmotic delivery system semipermeable body assembly in accordance with the present invention. As shown in FIG. 25, the insert 1060 is intended for insertion into the cylindrical recess or hollow interior portion 1052. The insert 1060 can be inserted in the recess 1052 for assisting the semipermeable body 1032 in effecting a seal with the interior of the enclosure 1071. In the embodiment of the present invention illustrated in FIG. 25, the insert 1060 is cylindrically shaped to match the shape of the ~~hollow interior portion~~ recess 1052, similar to the insert 60 shown in FIGS. 5 and 6. The insert 1060 may be in any number of different shapes and sizes. For example, the insert can be entirely conical, or as illustrated by FIG. 24, the insert 1060′ can be bullet-shaped. Thus, the insert 1060′ includes a conical portion 1063′ and a cylindrical portion 1061′. In the embodiments of the present invention illustrated in FIGS. 26 and 27, an insert (not illustrated) may be received by the recesses 2052, 2052′. As described above, because the semipermeable body 2032, 2032′ will deflect upon insertion into the enclosure 2071, the insert can be volumetrically smaller than the recess 2052, 2052′ and/or shaped differently than the recess 2052, 2052′ to accommodate the deflection of the semipermeable body toward the interior of the enclosure 2071, while still

assisting in effecting a seal between the enclosure and the semipermeable body 2032, 2032′. The insert 1060′ shown in FIG. 24 can be received by a substantially identically shaped cone-shaped recess 1052′. The inserts 1060, 1060′ can be fabricated from the same materials as the previously described insert 60.

Please replace paragraph number **[00221]** with the following rewritten paragraph:

[00221] When the osmotic delivery system plug 130 (see FIG. 12) is completely inserted into an opening of an enclosure of an osmotic delivery system, such as the opening 2079 shown in FIG. 28, the flat ~~circular~~ or end surface 148 is the liquid contact surface or exposure surface, i.e., the surface that is immediately exposed to liquid when the osmotic delivery system is located in its environment of use. The surface area A_o of the flat ~~circular~~ or end surface 148 is equal to πr^2. In contrast, the surface area A_c of the cone-shaped exterior surface 1048, 1048′, 2048, 2048′ is equal to $\pi r(r^2 + h^2)^{1/2}$.

Please replace paragraph number **[00222]** with the following rewritten paragraph:

[00222] One skilled in the art will appreciate that when the plugs 130, 1030 are completely inserted into openings of identical enclosures, the exposure surface area A_c of the conical surface 1048 is greater than the exposure surface area A_o of the ~~circular~~ flat or end surface 148 (assuming that the radius r, which generally corresponds to the internal diameter of the enclosure 1071, is the same for both semipermeable bodies). For example, FIG. 29 is a graph illustrating the theoretical increase in surface area A_c (mm^2) for a conical surface of a semipermeable body (such as the conical surface 1048 of the semipermeable body 1032), and the theoretical increase in surface area A_o (mm^2) for a flat circular surface of a semipermeable body (such as the flat circular surface 148 of the semipermeable body 132), as the diameter of the base of the conical surface and the diameter (mm) of the flat circular surface correspondingly increase. The curves illustrated in FIG. 29 are based on the above-described surface area equations for A_c and A_o. As shown by FIG. 29, the surface area A_c for the conical surface is greater than the surface area A_o of the circular surface at all diameters.

Please replace paragraph number **[00223]** with the following rewritten paragraph:

[00223] Because the surface area A_c of the conical surface 1048 is greater than that of the flat circular surface 148, the liquid permeation rate through the semipermeable body 1030 will be greater than that through the semipermeable body 130 (assuming that the semipermeable bodies 130, 1030 have roughly the same effective thickness L). Accordingly, the liquid permeation rate through the semipermeable bodies of the present invention may be increased by increasing the surface area A of the semipermeable body that is immediately exposed to liquids upon insertion of the osmotic delivery system in ~~an~~ a liquid environment of use. For example, FIG. 30 illustrates the theoretical increase in beneficial agent release rate dMt/dt (μl/hour) from an osmotic delivery system having a semipermeable body having a conical surface area A_c (such as that illustrated in FIG. 23B) as the diameter of the semipermeable body increases. FIG. 30 also generally illustrates the actual increase in beneficial agent release rate dMt/dt (μl/hour) from an osmotic delivery system having a semipermeable body having a flat circular surface area A_o (such as that illustrated in FIG. 12) as the diameter of the semipermeable body increases. The calculations used to obtain the curves shown in FIG. 30 assume that both semipermeable bodies are completely inserted within an enclosure of an osmotic delivery system.

Please replace paragraph number **[00224]** with the following rewritten paragraph:

[00224] The curve illustrated in FIG. 30 corresponding to the semipermeable membrane body having a flat circular surface area A_o was obtained by testing an osmotic delivery system having a semipermeable membrane body similar to that illustrated in FIG. 12 (formed from PEBAX 23, having a 23 mil thickness, and a ~~10.5 %~~ 10.5% radial clearance where radial clearance is the amount of pressure it takes to push the semipermeable membrane body out of the enclosure as measured by the ratio of the ID of the enclosure divided by the OD of the membrane expressed as a percentage). The curve illustrated in FIG. 30 corresponding to the semipermeable membrane body having a conical surface area A_c was obtained by theoretically estimating how much the beneficial agent release rate dMt/dt would increase (based on the equations: $A_c = r(r^2 + h^2)^{1/2}$ and $dMt/dt = dV/dt \bullet C = \{P\ A\ \Delta\pi / L\} \bullet C$) if the flat circular surface area A_o were increased to the conical surface area A_c as shown in FIG. 29 for a given diameter. As

FIG. 30 illustrates, because the surface area A_c of a conical surface is greater than that of a flat circle, the liquid permeation rate through a semipermeable body having a conical surface will be greater than that through a semipermeable body having only a flat circular surface. Accordingly, the liquid permeation rate through the semipermeable bodies of the present invention may be increased by increasing the surface area A of the semipermeable body that is immediately exposed to liquids upon insertion of the osmotic delivery system in ~~an~~ a liquid environment of use.

Please replace paragraph number **[00227]** with the following rewritten paragraph:

[00227] As set forth above, the liquid permeation rate through the semipermeable membrane bodies of the present invention may be increased by increasing the surface area A of the semipermeable body that is immediately exposed to liquid when the osmotic delivery system is located in a liquid environment of use. For example, the exposure surface area A may be increased by forming the conical portion 1033 on the semipermeable body 1032. Because the exposure surface area A_c of the cone-shaped surface 1048 is greater than the exposure surface area A_o of the flat ~~circular~~ or end surface 148, the liquid permeation rate through the semipermeable membrane 1032 is greater than that of the semipermeable membrane 132. Hence, the beneficial agent delivery rate dMt/dt may be increased by increasing the surface area A of the semipermeable body that is immediately exposed to liquids when the osmotic delivery system is located in a liquid environment of use.

Please replace paragraph number **[00229]** with the following rewritten paragraph:

[00229] The osmotic delivery system plugs 1030, 1030′, 2030, 2030′ permit the administration of beneficial agents from osmotic delivery systems at rapid delivery rates over a relatively short period of time, even though the plugs may use a semipermeable material which, as measured against previous membrane plugs, has a low permeability coefficient. These low permeability coefficient membrane materials do not have high liquid uptake characteristics, and do not swell as dramatically as high uptake materials when liquid from the surrounding environment permeates through the membrane. Thus, the osmotic delivery plugs 1030, 1030′,

2030,~~2030'~~ 2030', that each include a~~hollow interior portion~~ recess 1052, 1052′, 2052, 2052′ and a cone-shaped exterior surface 1048, 1048′, 2048, 2048′ configured for a fast liquid permeation rate, do not overly swell and creep out of the capsule, or permit the osmotic agent to leak from the capsule. Furthermore, the osmotic delivery plug 1030, 1030′, 2030, 2030′ can be made from materials that are stable in biological environments, and do not significantly degrade over time, which could permit fluids, crystals, or powder within the interior of the enclosure to leak to the environment of use.

Please replace paragraph number **[00231]** with the following rewritten paragraph:

[00231] In the above described manner, the liquid permeation rate through~~he~~ the semipermeable membrane bodies 32, 132, 232, 332, 432, 632, 732, 732, 832,~~(932~~ 932, 932′, ~~932″)~~ 932″, 1032, 1032′, 2032, 2032′ can be controlled in the osmotic delivery devices illustrated in FIGS. 7, 13-20, 25 and 28. This is especially advantageous because one membrane material can be used for the semipermeable bodies, while still permitting the liquid permeation rate to be controlled or varied. Additionally, as described above, by varying the "effective thickness" L and/or the exposure surface area A of the semipermeable bodies, the liquid permeation rate through the semipermeable bodies, and hence the delivery rate of the beneficial agent from the osmotic delivery~~system~~ system, can be controlled. This is beneficial~~because~~ because, for example, different desired liquid permeation rates through the semipermeable bodies are obtainable from semipermeable bodies formed from the same material having the same permeability coefficient and liquid uptake characteristics. This is further beneficial because biocompatibility and toxicity tests need only be performed on one semipermeable material. Moreover, it is especially desirable that the beneficial agent delivery rate from the osmotic delivery system be easily controlled by simply varying the liquid permeation rate through the semipermeable body of any one of the alternative embodiments of the present invention described above.